Journal of Clinical Oncology, Vol 18, Issue 20 (October), 2000: 3513-3521

Homoharringtonine and Low-Dose Cytarabine in the Management of Late Chronic-Phase Chronic Myelogenous Leukemia

By Hagop M. Kantarjian, Moshe Talpaz, Terry L. Smith, Jorge Cortes, Francis J. Giles, Mary Beth Rios, Susie Mallard, James Gajewski, Anthony Murgo, Bruce Cheson, Susan O'Brien

From the Departments of Leukemia, Bioimmunotherapy,Biostatistics, and Blood and Bone Marrow Transplantation,M.D. Anderson Cancer Center, Houston, TX; and the National CancerInstitute, Bethesda, MD.

Address reprint requests to Hagop M. Kantarjian, MD,Department of Leukemia, Box 61, M.D. Anderson Cancer Center., 1515Holcombe Blvd, Houston, TX 77030; emailhkantarj@mdanderson.org.

ABSTRACT

PURPOSE: : To evaluate the efficacy andtoxicity profiles of a combination regimen of homoharringtonine (HHT)and low-dose cytarabine (ara-C) in patients with Philadelphiachromosome (Ph)-positive chronic myelogenous leukemia (CML) whohad experienced treatment failure with interferon alfa (IFNα)therapy.

PATIENTS AND METHODS: One hundred five patients were treated: 100 in chronicphase (15 with cytogenetic clonal evolution) and five in acceleratedphase. Their median age was 52 years; all had been treatedunsuccessfully with IFNα; 94% were in late chronic phase; 43% hadbeen exposed to ara-C and 11% had been exposed to HHT. Patientsreceived HHT 2.5 mg/m^2 by continuousinfusion daily for 5 days and ara-C 15mg/m^2 daily in two subcutaneous injectionsfor 5 days every 4 weeks. The outcome of the 100 patients in chronicphase was compared with

a previous study group of 73 patients treatedwith HHT alone.

RESULTS: Overall, the complete hematologic response (CHR) rate in chronic phasewas 72%; the cytogenetic response rate was 32% (major response, 15%;complete response, 5%). Toxicities were acceptable, mostly related tomoderate diarrhea (3%), headaches (3%), cardiovascular events (3%),and myelosuppression-associated complications (3% to 14%). With amedian follow-up period of 25 months, the estimated 4-year survivalrate was 55%. Response rates were identical with HHT plus ara-C versusHHT alone, but the survival was significantly longer with thecombination after accounting for differences in the study groups andby multivariate analysis.

CONCLUSION: The combination regimen of HHT and ara-C is effective andsafe in patients with CML who have experienced treatment failure withIFNα and needs to be investigated together with IFNα as partof front-line CML therapy. The addition of ara-C did not improve theresponse rates but may have improved survival, perhaps throughsuppression of clones related to diseasetransformation.

INTRODUCTION

SURVIVAL IN Philadelphia chromosome (Ph)-positivechronic myelogenous leukemia (CML) has improved with interferon alfa (IFNα) therapy and allogeneic stem-cell transplantation(SCT).[1-4] With IFNα regimens, the median survival is6 to 7 years. Prognosis is associated with patient riskgroup,[5,6] doseschedules of IFNα, combined therapies (eg, with low-dosecytarabine [ara-C]),[7-9] and the achievement and degree ofPh-suppression (cytogenetic response). By multivariate and landmarkanalyses, achievement of cytogenetic and major cytogenetic responses(Ph-positive metaphases < 35%) have been associated independentlywith survival prolongation.[8-12]

Improving on the state and duration of minimal diseaseburden (complete hematologic or cytogenetic response) in CML, as inother cancers, has become the target of many investigationalstrategies and a surrogate end point for long-termsurvival. Discovering agents or modalities that may suppressPh-positive cells is thus actively pursued. Patients who fail IFNαregimens and who are not eligible for allogeneic SCT have the optionof receiving hydroxyurea therapy or undergoing investigationalapproaches such as autologous SCT or new agents.

Homoharringtonine (HHT), a plant alkaloid, was firstinvestigated in China and reported to be active in leukemias.[13,14] Phase I and II studiesin the United States confirmed its antileukemic activity butdocumented a high incidence of cardiovascular complications withshort-infusion schedules[15,16] and with higher-dose continuous-infusionschedules (30% incidence of hypotension and arrhythmias).[17] However, definite activity wasobserved in acute myelogenous leukemia (AML), acute promyelocyticleukemia (APL), and myelodysplastic syndrome (MDS).[17-20] We hadinvestigated a lower-dose, longer-duration, continuous-infusionschedule of HHT (2.5 mg/m^2 daily for 10 to14 days instead of 5 to 9 mg/m^2 daily for 5to 7 days). This schedule abrogated the occurrence of cardiovascularcomplications including hypotensive events and arrhythmias, whichoccurred in less than 5% of patients with the new schedule.[20] This observation, together with thenoted antiproliferative effect of HHT, resulted in further studies ofthe new schedule in CML, an indolent disease that requires a safeschedule for long-term therapy. We subsequently reported on theefficacy of HHT alone in patients

with late chronic-phase CML(duration of disease more than 12 months), many of whom wereIFNα-resistant, and in sequence with IFNα in earlychronic-phase CML.[21,22] In both studies, significant anti-CMLefficacy was observed.

ara-C has shown activity in CML as a single agent and incombination with IFNα.[23-25] The mechanisms underlying the anti-CMLefficacy of HHT are unknown but may be mediated through an effect onthe apoptosis pathways.[26,27] HHT had also been reported to besynergistic with IFNα and with ara-C in preclinicalmodels.[27] The limitedtherapeutic options of patients with late chronic-phase CML whoexperience treatment failure with IFNα therapy and who are notcandidates for allogeneic SCT and the efficacy of both HHT and ara-Cin vitro[26-28] and in vivo[21-25] led to thecurrent investigation of HHT and low-dose ara-C combination inpatients who have failed IFNα regimens. The results are summarizedin thisstudy.

PATIENTSAND METHODS

Study Group

Adults with a diagnosis of Ph-positive CML were enteredonto the study after informed consent was obtained. Eligibilitycriteria were as follows: (1) age 15 years or older, (2) chronic- oraccelerated-phase CML disease,[29] (3) good performance status (Zubrod0 to 2), (4) treatment failure on an IFNα-containing regimen, (5)normal renal (creatinine < 2 mg/dL) and hepatic functions(bilirubin < 2 mg/dL), and (6) no evidence of severe cardiacdisease (class III or IV).

Treatment failure of IFNα-containing regimens wasdefined in one of three categories: (1) hematologic resistancereferred to failure to achieve at least a partial hematologic response(PHR) after 3 months or more of therapy, failure to achieve a completehematologic response (CHR) after 6 months or more of therapy, or lossof hematologic response after achieving CHR, with an increasing WBCcount greater than 12×10^9/L onoptimal IFNα therapy documented for at least 4 weeks; (2)cytogenetic resistance referred to failure to obtain a cytogeneticresponse (Ph-positive cells ≥ 90%) after 12 months or more oftherapy, or loss of cytogenetic response with return of Ph-positivecells to greater than 90%; and (3) severe grade 3 or 4 unacceptabletoxicity related to IFNα therapy. For hematologic or cytogeneticresistance, patients were required to have received IFNα at 5million U/m^2 daily or the maximum-tolerateddose. The median IFNα dose delivery in our studies was 5 millionU/m^2 daily with IFNα alone and morethan 3 million U/m^2 daily with IFNαcombinations. In the category of failure because of unacceptableIFNα-associated toxicity, no minimum dose or duration of therapywas specified, because some of these toxicities may not bedose-related and are life-threatening (eg, immune-mediatedthrombocytopenia, immune-mediated hemolysis, neurotoxicity, severedepression, cardiomyopathy, pulmonary failure, and so on).

Patients in blastic phase were not eligible (marrow orperipheral blasts ≥ 30%). Patients with cytogenetic clonalevolution as their only accelerated-phase feature were included in thechronic-phase analysis on the basis of their more favorable prognosisfrom previous analyses.[30,31] Late chronic phase of CML was defined astime from diagnosis to start of therapy of more than 12months.[1,2,6,9,25]

Characteristics of the study group are listed inTable 1. Theirmedian age was 52 years; 49% were females. All patients had previouslyreceived IFNα therapy; 54% were referred from outside theinstitution having experienced treatment failure with IFNα.IFNα treatment failure was attributed to

hematologic resistance(42 patients), lack of cytogenetic response after 12 months or more ofIFNα (25 patients), severe unacceptable toxicity with IFNα (18patients), resistance plus toxicity (16 patients), or other reasons(four patients). All 25 patients entered for lack of cytogeneticresponse had IFNα therapy discontinued and had evidence of activeCML disease (leukocytosis, thrombocytosis) at the time of initiationof HHT and ara-C therapy. Only six patients received therapy with aCML chronic-phase duration of less than 12 months: five had IFNαtherapy discontinued because of severe toxicities (two of them withresistance) and one because of hematologic resistance. Elevenpatients had previously received HHT on the front-line sequential HHTfollowed by IFNα maintenance (DM91-13)[22]; 45 patients had previously receivedara-C with IFNα.

View this table: Table 1. Characteristics of the Study Group (105 patients)
[in this window]
[in a new window]

All 105 patients had 95% to 100% Ph-positive metaphases atthe start of HHT and ara-C therapy. One hundred patients were inchronic phase, 15 of whom had cytogenetic clonal evolution. Thisincluded trisomy 8 (two patients), double Philadelphia (one patient),isochromosome 17 (one patient), and other abnormalities (11patients). Five patients had accelerated phase CML (basophilia ≥20%, two patients; blasts ≥ 15%, one patient; thrombocytopenia <100 x 10^9/L, twopatients).

Therapy

HHT was given at a dose of 2.5mg/m^2 by continuous infusion daily for 5days (days 1 to 5) together with ara-C 15mg/m^2 daily in two equal subcutaneous doses12 hours apart for 5 days (days 1 to 5). HHT was given either througha central-line catheter or through a peripheral-line catheter replacedevery 2 to 3 days. Therapy was repeated every 4 weeks. HHT and ara-Ctherapy was modified to achieve with each course a lowest granulocytecount of approximately 10^9/L, with aplatelet count greater than 50 x10^9/L. For this purpose, the modificationsin therapy were in the duration of treatment, ie, in the number ofdays of treatment (± 1 day), rather than in the daily dose ofHHT or ara-C. For example, a patient who had achieved a lowestgranulocyte count greater than 2 x10^9/L and lowest platelet count greaterthan 100 x 10^9/L on a course of HHTand ara-C given for n days will receive the next course of HHT andara-C for (n + 1) days. In contrast, a patient who had achieved alowest granulocyte count of less than 10^9/Lor a lowest platelet count of less than 50 x10^9/L on a course given for n days willreceive the next course of HHT and ara-C for (n - 1)days.

Therapy was discontinued for the following reasons: (1)evidence of resistance with the optimal acceptable dose schedule, (2)disease transformation, (3) unacceptable toxicity (grade 3 to 4) afterdose reductions were made, (4) availability of other better options(eg, allogeneic SCT), or (5) patient or physician choice (eg, in thecase of a lack of cytogenetic response after 12 months of therapy). Iftoxicity was due to a particular agent (eg, hypotension or headachewith HHT), then the daily dose in subsequent courses was reduced by25% for grade 2 persistent toxicity and by 50% for grade 3 to 4toxicities. Toxicity was graded according to the National CancerInstitute common toxicity criteria.[32]

Criteriaand Statistical Considerations

Response criteria were as previously described.[2,6] A CHR required a WBC countof less than 10 x 10^9/L withoutperipheral immature cells (blasts, promyelocytes, myelocytes), aplatelet count of 450 x 10^9/L orless, and disappearance of signs and symptoms of disease, includingpalpable splenomegaly. CHR was further classified by cytogeneticresponse based on best suppression of Ph-positive cells as

follows:complete, Ph-positive 0%; partial, Ph-positive 1% to 34%; and minor,Ph-positive 35% to 90%. A major cytogenetic response included completeand partial cytogenetic responses (Ph-positive < 35%). A PHR wasdefined as for CHR, but with persistence of peripheral immature cellsand/or splenomegaly or thrombocytosis (but 50% or less ofpretreatment).

Results of X^2 tests arepresented as an indication of association of pretreatmentcharacteristics with cytogenetic response outcomes. Survival estimateswere based on the method of Kaplan and Meier[33] and compared using the log-ranktest.[34] For purposes ofcomparing results of this trial to those obtained on the trial thatimmediately preceded it,[21]patients were classified into risk groups on the basis of acombination of four factors (age, performance status, interval fromCML diagnosis to treatment, and percentage of peripheral basophils)previously reported as determinants of prognosis in late chronic-phaseCML.[35]

RESULTS

Chronic-PhaseCML

One hundred patients had chronic-phase CML; 15 of them hadevidence of clonal evolution. All had evidence of active CML diseaseat the start of therapy (patients entered on therapy because ofcytogenetic resistance had IFNα therapy discontinued and wereexhibiting WBC or platelet count increases by the time HHT and ara-Ctherapy was started).

Among 85 patients with active chronic-phase disease butwithout clonal evolution, 61 (72%) achieved CHR, and 11 (13%) hadPHR. Cytogenetic response was noted in 26 patients (31%): major in 12(14%) and complete in four (5%) (Table 2).

View this table: Table 2. Response to Therapy in 105 Patients Treated
[in this window]
[in a new window]

Among 15 patients with evidence of clonal evolution, 11(73%) achieved CHR, three (20%) achieved a PHR, and one failed toachieve a response. A cytogenetic response was observed in six of the11 patients who had achieved CHR (55%; 40% of total); response wascomplete in one, partial in two, and minor in three patients. Clonalevolution disappeared in the patient achieving complete cytogeneticresponse and in two of three patients who had a minor cytogeneticresponse. One of the five patients who had CHR without Ph suppressionalso had complete suppression of the clonalevolution.

Accelerated-PhaseCML

Among five patients treated in accelerated-phase CML,three (60%) obtained CHR. One such patient achieved a completecytogenetic response.

SideEffects

Nonhematologic. Side effects of HHT and ara-C combination are listed inTable 3. Themost common side effects were diarrhea and headache during therapy,mostly attributable to HHT. They were rarely severe (two patients;2%). Other side effects such as skin rashes, nausea, vomiting,fatigue, and aches

were unusual. Of note, hypotension and arrhythmiaswere observed in only 4% of patients.

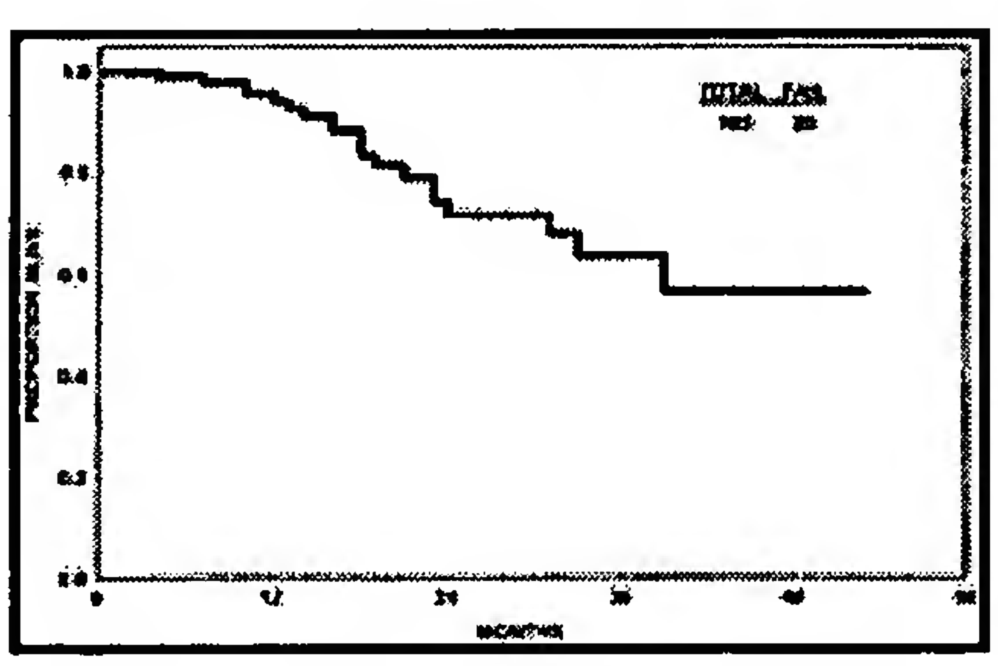
View this table: Table 3. Side Effects
[in this window]
[in a new window]

Hematologic. With induction therapy, the incidence of granulocytopenialess than 0.5 x 10^9/L was 13% and theincidence of thrombocytopenia less than 30 x10^9/L was 4%. Significant anemia withhemoglobin less than 9.0 g/dL occurred in14% during induction and in50% of patients (14% of courses) during maintenancetherapy.

Prognosis byPretreatment Characteristics
Responses in chronic phase by different pretreatmentcharacteristics are listed in Table 4. No significantassociations were found between cytogenetic response and knownprognostic features. There were no differences in response by durationof chronic-phase disease or by prior exposure to ara-C. Survival wassignificantly worse among older patients. A trend for worse survivalwas also observed with thrombocytosis, increased marrow blasts, andlonger duration of chronic phase (Table 4).

View this table: Table 4. Outcome Within Subsets Based on Pretreatment Characteristics
[in this window]
[in a new window]

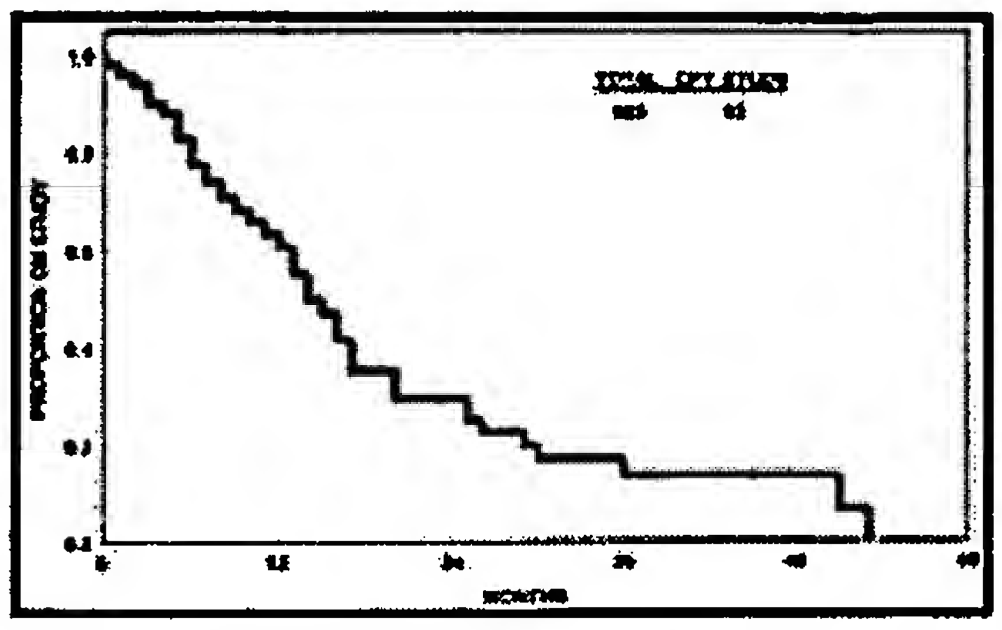
Follow-UpResults
The median number of HHT and ara-C courses was nine(range, one to 50 courses). The total number of courses received sofar was 1,071. With a median follow-up time of 25 months, 18 deathshave occurred, at times ranging from 5 to 39 months after the start oftherapy. The estimated survival rates at 2 and 4 years were 77% and55%, respectively (Fig1). The median time on therapy was 10 months(Fig 2). Atlast follow-up, 41 patients continued on therapy, and 64 were removedfrom study for reasons listed in Table 5.



View larger version (11K):
[in this window]
[in a new window]

Fig1. Overall survival from start of

Fig2. Time on



View larger version (12K):
[in this window]
[in a new window]

View this table: Table 5. Patient Status (N = 105 Patients)
[in this window]
[in a new window]

The course of patients who achieved a major cytogeneticresponse is listed in Table6. At the time of last follow-up, seven of the 16patients with cytogenetic response (44%) continued to have acytogenetic response: two were still in CHR on therapy, threedeveloped hematologic resistance, and four were removed from studybecause of toxicity (two patients), patient request (one patient), andcatheter-related problems (one patient). Two of 16 cytogeneticresponders died (one after allogeneic transplantation) compared with18 of 89 patients without a cytogenetic response.

View this table: Table 6. Follow-Up of Patients With Major Cytogenetic Response
[in this window]
[in a new window]

Comparisonof HHT Plus Ara-C to Previous HHT alone

To evaluate the possible impact on survival of addingara-C to HHT, we compared the results of the 100 patients in chronicphase for this trial with the previous trial of HHT alone, whichaccrued 73 patients with late chronic-phase CML. That trial wasconducted starting in 1989 and had identical eligibility requirementsto the HHT plus ara-C trial, except that there was no prior exposureto HHT or ara-C (not available then) and prior IFNα treatmentfailure was not required. Compared with the 100 patients in chronicphase receiving HHT plus ara-C, the patients treated with HHT alonewere younger (P = .07),but had a higher incidence of splenomegaly (P = .06) and leukocytosis(P = .002) and a higherincidence of peripheral blasts (P = .001) and clonal evolution(P = .03)(Table 7).

View this table: Table 7. Comparison of HHT Versus HHT Plus Ara-C Study Group
[in this window]
[in a new window]

Although there were differences in distributions ofpatient characteristics between the two trials (Table 7), a categorization ofpatients into risk groups based on four factors previously identifiedas important for prognosis in late chronic-phase CML[35] suggested that patients on the twostudies had similar overall

prognosis. A slightly higher proportion ofpatients receiving HHT alone fell in the lowest risk group, havingnone of the unfavorable factors (age ≥ 60 years, time fromdiagnosis to treatment ≥ 3 years, performance status of ≥ 1, orperipheral-blood basophils ≥ 7%). Response rates were nearlyidentical on the two trials (Table 7), but early resultssuggested that survival was somewhat prolonged for patients treatedwith HHT plus ara-C (Fig3; *P*= .04 [test stratified by risk group]). Similarresults were obtained with stratification by age and platelets(*P* = .03).

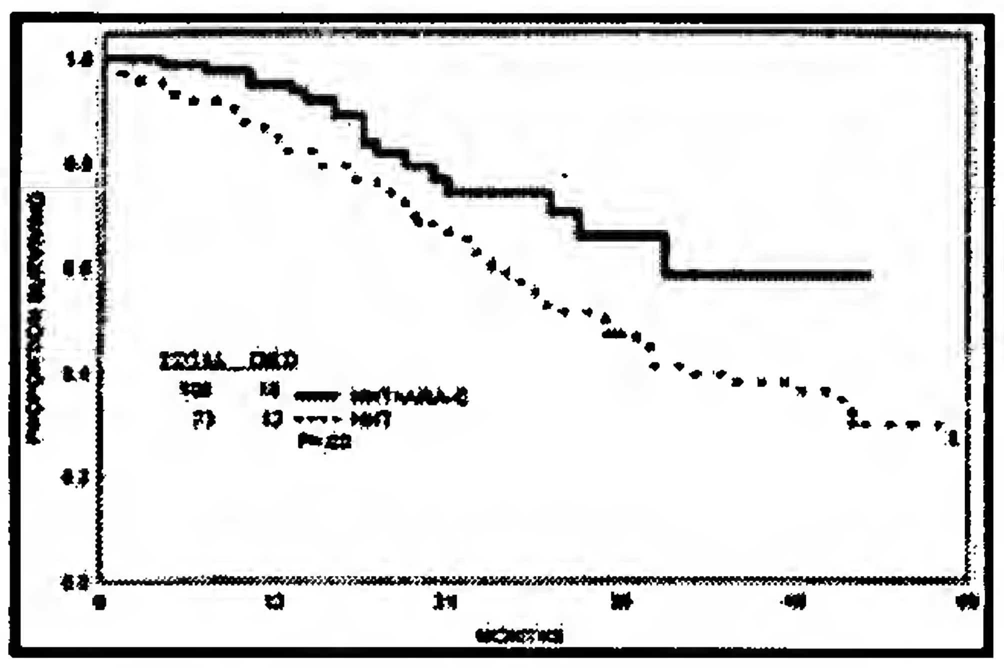


Fig3. Survival with HHT with or without

View larger version (14K):
[in this window]
[in a new window]

We also analyzed all 173 patients in a multivariateanalysis to investigate possible associations of pretreatmentcharacteristics with survival, and we included therapy (HHT *v* HHT plus ara-C) as a prognosticvariable. The multivariate analysis selected older age (*P* = .01), splenomegaly (*P* < .01), and thrombocytosis(*P* = .02) asindependent poor significant factors, but therapy remained animportant prognostic factor (*P*= .026) favoring the addition ofara-C.

DISCUSSION

▲ TOP
▲ ABSTRACT
▲ INTRODUCTION
▲ PATIENTSAND METHODS
▲ RESULTS
▪ DISCUSSION
▼ REFERENCES

The combination of HHT and ara-C in patients who hadexperienced treatment failure with IFNα yielded encouragingresults. Among patients treated in chronic phase, 72% achieved CHR;31% achieved a cytogenetic response, which was majorin14%. Considering that the study group included mostlyIFNα-resistant patients in late chronic phase who had fewtherapeutic options available, the median duration of disease controlof 10 months and estimated 4-year survival rate of 55% werefavorable. Our results suggest that HHT-based regimens may beeffective therapies for patients for whom IFNα therapy wasunsuccessful and who are not candidates for allogeneic SCT. They alsoindicate a potential role of HHT and ara-C as part of front-line CMLtherapy to improve the degree and duration of cytogenetic response andthe prognosis of patients with CML. Considering the acceptabletoxicity profile of the regimen, such investigational strategies maybe appropriate.

Comparable or even better results have also been reportedby Ernst et al,[36] who usedHHT 2.5 mg/m^2 daily and ara-C 7.5mg/m^2 daily by continuous infusion for upto 14 days. In their report, the CHR rate among 44 patients treatedwas 93%, and cytogenetic responses were observed in 16 (44%) of 36patients treated for at least 6 months. Their study group included 14patients in early chronic-phase CML: all 14 (100%) achieved CHR, and11 (84%) of 13 assessable patients had a major

cytogeneticresponse. It is not clear how much prior IFNα therapy thesepatients had received and whether they were clearly IFNα-resistantor had been entered onto the study because of unacceptableIFNα-related toxicities. The comparison of response rates withinsimilar patient subcategories would be of interest. Their studysuggested that even better CHR and cytogenetic response rates may beexpected depending on patient selection (eg, IFNα toxic patients,early chronic-phase CML), as had also been observed in our previousstudy of HHT (six courses followed by IFNα maintenance) in earlychronic-phase CML.[22]

An important question is the additional benefit of ara-Ccombined with HHT. Although we attempted to compare the twosequential studies at our institution (HHT alone in 73 patients withactive disease [21 of whom had clonal evolution] and thecurrent study with HHT plus ara-C), the comparison and evaluation ofthe benefit from addition of ara-C was difficult because ofdifferences in the study groups (Table 7), dose schedules, andfollow-up times. HHT alone was used for 10 to 14 days during remissioninduction and for 7 days every month during maintenancetherapy. Patients previously treated with HHT alone had been lessheavily pretreated with IFNα and had not been exposed to eitherHHT or to ara-C. However, it seems that the HHT plus ara-C combinationwas not associated with an increased risk of known or unpredictableside effects and may have improved outcome in CML after accounting forknown differences in prognostic factors within the two studygroups. The possible beneficial effect of ara-C on survival may bemediated through suppression of clones responsible for diseasetransformation.

Two issues, if resolved, may expand the potential use ofHHT in hematologic and perhaps solid tumors: (1) the route-scheduledelivery, and (2) the mechanisms underlying the cardiovascular sideeffects with shorter infusion schedules. The continuous-infusionschedule, although effective against CML, is cumbersome and limits theinvestigation of even lower-dose longer-exposure schedules (eg, 0.5 to1 mg/m^2 for 3 to 4 weeks). A safesubcutaneous schedule may allow reinvestigating HHT, not only in CML,but also as maintenance therapy in AML, as differentiation therapy inAPL, and as a chronic subcutaneous low-dose schedule in MDS. All ofthese are diseases in which HHT investigations had been discouragedbecause of the HHT toxicity profile, despite evidence ofefficacy.[17-20,37] Understanding the etiology of thecardiovascular problems may allow a targeted development of a newgeneration of HHT derivatives designed to avoid cardiovascular sideeffects and to expand the spectrum of antitumor activity (as has beenshown for deoxynucleoside cytidine analogs, eg, ara-C *v* gemcitabine). This will thenrejuvenate anticancer research with HHT-like molecules.

HHT has shown activity in hematologic cancers other thanCML and AML that needs further exploration. Low-dose harringtonine wasreported to induce remissions in APL.[37] Ten patients with APL receivedharringtonine 1 to 3 mg over 4 to 5 hours daily until completeresponse; seven (70%) achieved complete response after a median of 71days and a median cumulative dose of 136 mg. HHT has already shown invitro effects on apoptosis and differentiation,[26,27,38] which mayprove helpful not only against APL but also against other cancerswhere maturation arrest is pathophysiologic, such as MDS. Among 15patients with MDS treated by Feldman et al,[19] four (27%) achieved objectiveresponses. Myelosuppressive complications were significant at the doseschedule used (5 mg/m^2 by continuousinfusion daily for 9 days), and a high mortality rate precludedfurther investigations with this schedule.[19] Lower dose schedules of HHT, as inCML, may prove effective and less toxic in theseconditions.

Recent studies have reported encouraging results with anew *BCR-ABL* tyrosine kinaseinhibitor, STI-571. Among patients treated in chronic-phase CML whohad experienced treatment failure with IFNα (because of resistanceor toxicity), the CHR rate was 100% when STI-571 was given at 300 mgor more orally

daily; cytogenetic responses were alsoobserved. STI-571 was also beneficial in the treatment ofaccelerated-blastic phases of CML.[39,40] Future studies will better define therelative benefits of STI-571 and HHT plus ara-C, alone or incombinations, in patients who have been treated unsuccessfully withIFN α.

In summary, the combination of HHT and low-dose ara-C wassafe and effective in the dose schedule used in our study in patientswith late chronic-phase CML. This now offers such patients (ifIFNα treatment had failed) a good treatment option and indicatesthat further studies with IFNα in front-line CML therapy arewarranted.

REFERENCES

1. KantarjianHM, O'Brien S, AnderliniP, et al:Treatment of myelogenous leukemia: Current status and investigationaloptions. Blood 87:3069-3081, 1996 [Free Full Text]
2. KantarjianHM, Giles FJ, O'BrienSM, et al:Clinical course and therapy of chronic myelogenous leukemiawith interferon-alpha and chemotherapy. Hematol Oncol Clin North Am 12:31-80, 1998[Medline]
3. GoldmanJM, Szydlo R, HorowitzMM, et al:Choice of pre-transplant treatment and timing oftransplants for chronic myelogenous leukemia in chronicphase. Blood 82:2235-2238, 1993 [Abstract]
4. GratwohlA, Hermans J, NiederwieserD, et al:Bone marrow transplantation for chronic myeloid leukemia: Long-term results—Chronic LeukemiaWorking Party of the European Group for Bone MarrowTransplantation. Bone MarrowTransplant 12:509-516, 1993[Medline]
5. HehlmannR, Ansari H, Hasford, et al:Comparative analysis of the impact of risk profile and ofdrug therapy on survival in CML using Sokal's index and a newscore: German Chronic Myeloid Leukaemia(CML) Study Group. Br J Haematol 97:76-85, 1997[Medline]
6. KantarjianHM, Smith TL, O'BrienS, et al:Prolonged survival in chronic myelogenous leukemia aftercytogenetic response to interferon-alpha therapy. Ann Intern Med 122:254-261, 1995 [Abstract/Free Full Text]
7. GuilhotF, Chastang C, MichalletM, et al:Interferon alfa-2b combined with cytarabine versusinterferon alone in chronic myelogenous leukemia: French Chronic Myeloid Leukemia StudyGroup. N Engl J Med 337:223-229, 1997[Abstract/Free Full Text]
8. TuraS: Cytarabine increases karyotypic response in alpha-IFNtreated chronic myeloid leukemia patients: Results of a national prospective randomized trial. Blood 92: 317, 1998 (abstr)
9. KantarjianHM, O'Brien S, SmithT, et al:Treatment of Philadelphia chromosome-positive early chronicphase chronic myelogenous leukemia with daily doses of interferonalpha and low-dose cytarabine. J ClinOncol 17:284-292, 1999[Abstract/Free Full Text]
10. The Italian Cooperative StudyGroup on Chronic Myeloid Leukemia :Interferon alfa-2a as compared with conventional chemotherapy for thetreatment of chronic myeloid leukemia. N Engl J Med, 330:820-825, 1994
11. AllanNC, Richards SM, ShepherdPC: UKMedical Research Council randomized, multicenter trial ofinterferon-alpha n1 for chronic myeloid leukaemia: Improved survival irrespective of cytogeneticresponse—The UK Medical Research Council's Working Partiesfor Therapeutic Trials in Adult Leukemia. Lancet 345:1392-1397, 1995[Medline]
12. Chronic Myeloid LeukemiaTrialists' Collaborative Group :Interferon alfa versus chemotherapy for chronic myeloid leukemia: Ameta-analysis of seven randomized trials. J Natl Cancer Inst, 89:1616-1620, 1997
13. Cephalotaxus ResearchCoordinating Group: Cephalotaxine esters inthe treatment of acute leukemia: Apreliminary clinical assessment. Chin Med J 2:263-272, 1976[Medline]
14. Chinese People's Liberation Army 18thHospital: On the treatment of leukemias: Clinical analysis

of 72cases. Zhonghua Yizue Zazhi, 58:163, 1978(abstr)
15. LeghaSS, Keating M, PicketS, et al:Phase I clinical investigation of homoharringtonine. Cancer Treat Rep 68:1085-1091, 1984[Medline]
16. NeidhartJA, Young DC, KrautE, et al:Phase I trial of homoharringtonine administered byprolonged continuous infusion. CancerRes 46:967-969, 1986[Abstract]
17. WarrellRP Jr, Coonley CJ, GeeTS: Homoharringtonine: An effectivenew drug for remission induction in refractory non-lymphoblasticleukemia. J Clin Oncol 3:617-621, 1985[Abstract]
18. FeldmanE, Arlin Z, AhmedT, et al:Homoharringtonine is safe and effective for patients withacute myelogenous leukemia (I). Leukemia 6:1185-1188, 1992[Medline]
19. FeldmanEJ, Seiter KP, AhmedT, et al:Homoharringtonine in patients with myelodysplastic syndrome(MDS) and MDS evolving to acute myeloid leukemia. Leukemia 10:40-42, 1996 [Medline]
20. KantarjianH, Keating M, McCredieK, et al:Phase II study of homoharringtonine in refractory acutemyelogenous leukemia. Cancer 63:813-817, 1989[Medline]
21. O'BrienS, Kantarjian H, KeatingM, et al:Homoharringtonine therapy induces responses in patientswith chronic myelogenous leukemia in late chronic phase. Blood 86:3322-3326, 1995 [Abstract/Free Full Text]
22. O'BrienS, Kantarjian H, KollerC, et al:Sequential homoharringtonine and interferon-alpha in thetreatment of early chronic phase chronic myelogenousleukemia. Blood 93:4149-4153, 1999 [Abstract/Free Full Text]
23. SokalJ, Beingner SH: Low-dose cytosine arabinoside bysubcutaneous infusion in early and advanced chronic granulocyticleukemia. Blood 68: 233a, 1986 (abstr)
24. RobertsonMJ, Tantravahi R, GriffinJD, et al:Hematologic remission and cytogenetic improvement aftertreatment of stable-phase chronic myelogenous leukemia with continuousinfusion of low-dose cytarabine. Am JHematol 43:95-102, 1993[Medline]
25. KantarjianH, Keating M, EsteyE, et al:Treatment of advanced Philadelphia chromosome-positivechronic myelogenous leukemia with interferon-alpha and low-dosecytarabine. J Clin Oncol 10:772-778, 1992[Abstract]
26. VisaniG, Russo D, OttavianiE, et al:Effects of homoharringtonine alone and in combination withalpha interferon and cytosine arabinoside on in vitro growth andinduction of apoptosis in chronic myeloid leukemia and normalhematopoietic progenitors. Leukemia 11:624-628, 1997 [Medline]
27. O'BrienS, Keating A, KantarjianH, et al:Homoharringtonine induces apoptosis in chronic myelogenousleukemia cells. Blood 82:555a, 1993 (abstr, suppl 1)
28. SokalJ, Leong SS, GomezGA: Preferential inhibition by cytarabine of CFU-GM frompatients with chronic granulocytic leukemia. Cancer 59:197-202, 1987[Medline]
29. KantarjianHM, Dixon D, KeatingMJ, et al:Characteristics of accelerated disease in chronicmyelogenous leukemia. Cancer 61:1441-1446, 1988[Medline]
30. MajlisA, Smith TL, TalpazM, et al:Significance of cytogenetic clonal evolution in chronicmyelogenous leukemia. J Clin Oncol 14:196-203, 1996[Abstract]
31. CortesJ, Talpaz M, O'BrienS, et al:Suppression of cytogenetic clonal evolution with interferonalfa therapy in patients with Philadelphia chromosome-positive chronicmyelogenous leukemia. J Clin Oncol 16:3279-3285, 1998[Abstract]
32. National CancerInstitute : Guidelines for reporting ofadverse drug reactions. Bethesda, MD, Division of Cancer Treatment, National CancerInstitute, 1988
33. KaplanEL, Meier P: Nonparametric estimation fromincomplete observation. J Am StatAssoc 58:457-481, 1958
34. MantelN: Evaluation of survival data and two new rank orderstatistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966[Medline]
35. RodriguezJ, Cortes J, SmithTL, et al:Determinants of prognosis in late chronic-phase chronicmyelogenous leukemia. J Clin Oncol 16:3782-3787, 1998[Abstract]
36. ErnstTJ, Vance E, AlyeaE III, et al:Homoharringtonine and low-dose Ara-C is a highly effectivecombination for the treatment of CML in chronic phase. Blood 90: 517a, 1997 (abstr, suppl1)
37. Jing-SongY, Xiao-Hong W, Guang-HuiF, et al:Small dose harringtonine induces complete remission inpatients with acute promyelocytic leukemia. Leukemia 2:427-429, 1988[Medline]
38. BoydAW, Sullivan JR: Leukemic cell differentiation invivo and in vitro: Arrest of proliferationparallels the differentiation induced by the antileukemic drugharringtonine. Blood 6:384-392, 1984

The present invention describes a new method of therapy, its use/application in human and animal diseases and disorders, particularly cancers, leukemias, lymphomas, parasite diseases and therapeutic resistance to other agent, by the subcutaneous mode of administration of a drug based upon harringtonines such as homoharringtonine or harringtonine their salt and tautomeric form eventually combined with one or more chemotherapeutic agents or inhibitor of resistance, using a specifically adapted formulation in which (i) the pH of the formulation or constituted solution for injection ranges between 5.5 and 8.5, (ii) the harringtonines are solution or hydrophilic freeze-dried powder ready-to-reconstitute of buffered salt of homoharringtonine or harringtonine and, (iii) the level of chromatographic purity of harringtonines suitable for pharmaceutical use is higher than 99.7%.

39. DrukerBJ, Talpaz M, RestaD, et al:Clinical efficacy and safety of an ABL specific tyrosinekinase inhibitor as targeted therapy for chronic myelogenous leukemia. Blood 94: 368a, 1999 (abstr, suppl1)
40. DrukerBJ, Kantarjian H, SawyersCL, et al:Activity of an ABL specific tyrosine kinase inhibitor inpatients with BCR-ABL positive acute leukemias, including chronicmyelogenous leukemia in blast crisis. Blood 94: 697a, 1999 (abstr, suppl1)

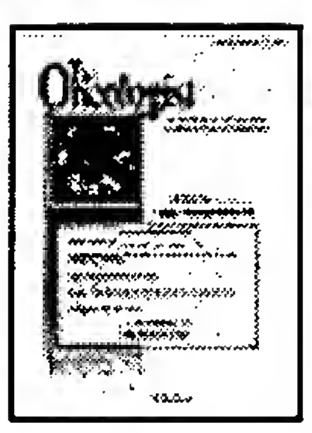
Submitted January 24, 2000; accepted June 6, 2000.

This article has been cited by other articles:

(Search Google Scholar for Other Citing Articles)

Clinical Cancer Research ▶HOME

F. Giles, S. Verstovsek, D. Thomas, S. Gerson, J. Cortes, S. Faderl, A. Ferrajoli, F. Ravandi, S. Kornblau, G. Garcia-Manero, E. Jabbour, S. O'Brien, V. Karsten, A. Cahill, K. Yee, M. Albitar, M. Sznol, and H. Kantarjian
Phase I Study of Cloretazine (VNP40101M), a Novel Sulfonylhydrazine Alkylating Agent, Combined with Cytarabine in Patients with Refractory Leukemia
Clin. Cancer Res., November 1, 2005; 11(21): 7817 - 7824.
[Abstract] [Full Text] [PDF]

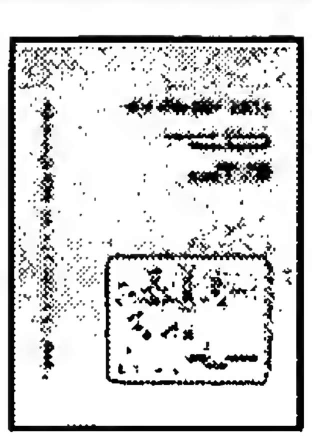


The Oncologist ▶HOME

R. M. Stone
Optimizing Treatment of Chronic Myeloid Leukemia: A Rational Approach
Oncologist, June 1, 2004; 9(3): 259 - 270.
[Abstract] [Full Text] [PDF]

blood ▶HOME

H. M. Kantarjian, M. Talpaz, S. O'Brien, F. Giles, G. Garcia-Manero, S. Faderl, D. Thomas, J. Shan, M. B. Rios, and J. Cortes
Dose escalation of imatinib mesylate can overcome resistance to standard-dose therapy in patients with chronic myelogenous leukemia
Blood, January 15, 2003; 101(2): 473 - 475.
[Abstract] [Full Text] [PDF]



HEMATOLOGY ▶HOME

B. J. Druker, S. G. O'Brien, J. Cortes, and J. Radich
Chronic Myelogenous Leukemia
Hematology, January 1, 2002; 2002(1): 111 - 135.
[Abstract] [Full Text]

Clinical Cancer Research ▸HOME

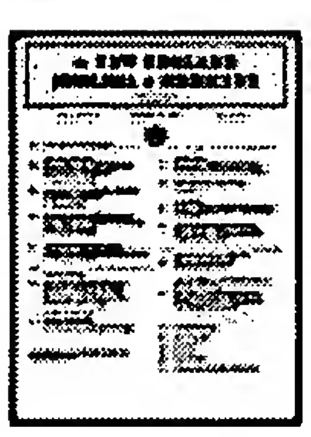
H. M. Kantarjian, S. O'Brien, J. E. Cortes, T. L. Smith, M. B. Rios, J. Shan, Y. Yang, F. J. Giles, D. A. Thomas, S. Faderl, G. Garcia-Manero, S. Jeha, W. Wierda, J.-P. J. Issa, S. M. Kornblau, M. Keating, D. Resta, R. Capdeville, and M. Talpaz
Treatment of Philadelphia Chromosome-positive, Accelerated-phase Chronic Myelogenous Leukemia with Imatinib Mesylate
Clin. Cancer Res., July 1, 2002; 8(7): 2167 - 2176.
[Abstract] [Full Text] [PDF]

blood ▸HOME

H. M. Kantarjian, J. Cortes, S. O'Brien, F. J. Giles, M. Albitar, M. B. Rios, J. Shan, S. Faderl, G. Garcia-Manero, D. A. Thomas, D. Resta, and M. Talpaz
Imatinib mesylate (STI571) therapy for Philadelphia chromosome-positive chronic myelogenous leukemia in blast phase
Blood, May 15, 2002; 99(10): 3547 - 3553.
[Abstract] [Full Text] [PDF]

blood ▸HOME

M. Talpaz, R. T. Silver, B. J. Druker, J. M. Goldman, C. Gambacorti-Passerini, F. Guilhot, C. A. Schiffer, T. Fischer, M. W. N. Deininger, A. L. Lennard, A. Hochhaus, O. G. Ottmann, A. Gratwohl, M. Baccarani, R. Stone, S. Tura, F.-X. Mahon, S. Fernandes-Reese, I. Gathmann, R. Capdeville, H. M. Kantarjian, and C. L. Sawyers
Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study
Blood, March 15, 2002; 99(6): 1928 - 1937.
[Abstract] [Full Text] [PDF]



The NEW ENGLAND JOURNAL of MEDICINE ▸HOME

H. Kantarjian, C. Sawyers, A. Hochhaus, F. Guilhot, C. Schiffer, C. Gambacorti-Passerini, D. Niederwieser, D. Resta, R. Capdeville, U. Zoellner, M. Talpaz, B. Druker, and the International STI571 CML Study Group
Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia
N. Engl. J. Med., February 28, 2002; 346(9): 645 - 652.
[Abstract] [Full Text] [PDF]

JOURNAL OF CLINICAL ONCOLOGY ▸HOME

F. J. Giles, G. Garcia-Manero, J. E. Cortes, S. D. Baker, C. B. Miller, S. M.

O'Brien, D. A. Thomas, M. Andreeff, C. Bivins, J. Jolivet, and H. M. Kantarjian
Phase II Study of Troxacitabine, a Novel Dioxolane Nucleoside Analog, in Patients With Refractory Leukemia
J. Clin. Oncol., February 1, 2002; 20(3): 656 - 664.
[Abstract] [Full Text] [PDF]

This Article

- Abstract FREE
- Full Text (PDF)
- Alert me when this article is cited
- Alert me if a correction is posted

Services

- Email this article to a colleague
- Similar articles in this journal
- Similar articles in PubMed
- Alert me to new issues of the journal
- Save to my personal folders
- Download to citation manager

Google Scholar

- Articles by Kantarjian, H. M.
- Articles by O'Brien, S.
- Articles citing this Article

PubMed

- PubMed Citation
- Articles by Kantarjian, H. M.
- Articles by O'Brien, S.

Journal of Clinical Oncology, Vol 3, 617-621, Copyright © 1985 by American Society of Clinical Oncology

ARTICLES

Homoharringtonine: an effective new drug for remission induction in refractory nonlymphoblastic leukemia

RP Warrell Jr, CJ Coonley and TS Gee

Homoharringtonine (HHT) is a new plant alkaloid originally isolated in the People's Republic of China. Preliminary studies have suggested antitumor activity in several neoplastic diseases. We treated 49 patients with relapsed or resistant acute leukemia with escalating doses of homoharringtonine administered by continuous infusion. Three dose levels were examined: 5 mg/m2 for seven days, 7 mg/m2 for seven days, and 5 mg/m2 for nine days. Of 28 patients with acute nonlymphoblastic leukemia who received cumulative doses of 45 to 49 mg/m2, seven patients (25%) achieved complete remission. Four of these remissions occurred in a subset of ten patients previously resistant to two or more induction attempts with conventional chemotherapy. There were no remissions in three patients with secondary leukemia or in seven patients with acute lymphoblastic leukemia. Reversible hypotension, fluid retention, diarrhea, and tumor lysis syndrome were the major toxic effects of this treatment. Our results indicate that homoharringtonine is an effective new drug for the treatment of acute nonlymphoblastic leukemia and that this drug does not share cross- resistance with conventional antileukemic agents. The recommended dose is 5 mg/m2/d administered by continuous infusion for nine days.

This article has been cited by other articles:

(Search Google Scholar for Other Citing Articles)

JOURNAL OF CLINICAL ONCOLOGY ▸HOME

H. M. Kantarjian, M. Talpaz, T. L. Smith, J. Cortes, F. J. Giles, M. B. Rios, S. Mallard, J. Gajewski, A. Murgo, B. Cheson, and S. O'Brien

Google Scholar BETA

Search | Advanced Scholar Search | Scholar Preferences | Scholar Help

Scholar Results **1** - **10** of about **11** citing **Warrell: Homoharringtonine: an effective new drug for remissioi**

Homoharringtonine and low-dose cytarabine in the management of late chronic-phase chronic ...
HM Kantarjian, M Talpaz, TL Smith, J Cortes, FJ ... - J Clin Oncol, 2000 - jco.org
Search for: Limit by: All Topics ...
Cited by 34 - Web Search - jco.org - ncbi.nlm.nih.gov

History, Current Research, and Future Directions
HM Kantarjian, M Talpaz, V Santini, A Murgo, B ... - CANCER, 2001 - doi.wiley.com
Page 1. Homoharringtonine History, Current Research, and Future Directions
Hagop M. Kantarjian, MD 1 Moshe Talpaz, MD 1 Valeria Santini ...
Cited by 17 - Web Search - doi.wiley.com - ncbi.nlm.nih.gov

In vitro effects of STI 571-containing drug combinations on the growth of Philadelphia-positive ...
B Scappini, F Onida, HM Kantarjian, L Dong, S ... - Cancer, 2002 - doi.wiley.com
Page 1. In Vitro Effects of STI 571-Containing Drug Combinations on the Growth
of Philadelphia-Positive Chronic Myelogenous Leukemia Cells ...
Cited by 15 - Web Search - ncbi.nlm.nih.gov

Simultaneous homoharringtonine and interferon-in the treatment of patients with chronic-phase ...
SO'Brien, M Talpaz, J Cortes, J Shan, FJ Giles, ... - Cancer, 2002 - doi.wiley.com
Page 1. Simultaneous Homoharringtonine and Interferon- in the Treatment
of Patients with Chronic-Phase Chronic Myelogenous Leukemia ...
Cited by 13 - Web Search - doi.wiley.com - ncbi.nlm.nih.gov

A phase II study of homoharringtonine for the treatment of children with refractory or recurrent ...
BA Bell, MN Chang, HJ Weinstein - Medical and Pediatric Oncology, 2001 - doi.wiley.com
Page 1. Med Pediatr Oncol 2001;37:103±107 A Phase II Study of Homoharringtonine
for the Treatment of Children With Refractory or Recurrent Acute Myelogenous ...
Cited by 6 - Web Search - doi.wiley.com - ncbi.nlm.nih.gov

Etoposide-resistant human colon and lung adenocarcinoma cell lines exhibit sensitivity to ...
LJ Wilkoff, EA Dulmadge, G Vasanthakumar, JP ... - Cancer Chemotherapy and Pharmacology, 1993 - springerlink.com
Page 1. Cancer Chemother Pharmacol (1993) 33: 149-153 ancer hemotherapy
and harmacology 9 Spfinger-Verlag 1993 Etoposide-resistant ...
Cited by 3 - Web Search - ncbi.nlm.nih.gov

Promising approaches in acute leukemia
J Cortes, HM Kantarjian - Investigational New Drugs, 2000 - kluweronline.com
Page 1. Investigational New Drugs 18: 57–82, 2000. © 2000 Kluwer Academic
Publishers. Printed in the Netherlands. 57 Invited review ...
Cited by 1 - Web Search - springerlink.com - ncbi.nlm.nih.gov

Metabolism of homoharringtonine, a cytotoxic component of the evergreen plant Cephalotaxus ...

D Ni, DH Ho, M Vijjeswarapu, E Felix, P Robyn Rhea ... - Journal of Experimental Therapeutics and Oncology, 2003 - blackwell-synergy.com
Full Article. View/Print PDF article (151K). Download to reference manager.
Journal of Experimental Therapeutics and Oncology Volume ...
Cited by 1 - Web Search - ingentaconnect.com - ncbi.nlm.nih.gov

Homoharringtonine mediates myeloid cell apoptosis via upregulation of pro-apoptotic bax and inducing ...
L Yinjun, J Jie, X Weilai, T Xiangming - American Journal of Hematology, 2004 - doi.wiley.com
Page 1. Homoharringtonine Mediates Myeloid Cell Apoptosis via Upregulation of
Pro-apoptotic bax and Inducing Caspase-3-Mediated Cleavage of Poly(ADP-ribose) ...
Cited by 1 - Web Search - ncbi.nlm.nih.gov

Adult Acute Myeloid Leukemia
TO Overview - jncicancerspectrum.oupjournals.org
Content Sources... ...
Web Search

Google ▶
Result Page: 1 2 **Next**

Search

Google Home - About Google - About Google Scholar

Generate Collection | Print

Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. 20040006064. 01 Apr 03. 08 Jan 04. Cephalotaxanes, their method of preparation and their use in treatment of cancers, leukemias, parasites including those resistant to usual chemotherapeutic agents and as reversal agents. Robin, Jean-Pierre, et al. 514/214.01; 540/579 A61K031/55 C07D487/02.

☐ 2. 20020128258. 09 Mar 01. 12 Sep 02. Therapeutical method involving subcutaneous administration of drugs containing cephalotaxine derivatives. Robin, Jean-Pierre, et al. 514/214.01; A61K031/55.

☐ 3. H000271. 18 Dec 85; 05 May 87. Treatment of malaria with esters of cephalotaxine. Whaun; June M.. 514/214.01;. A61K031/55 .

Generate Collection | Print

Terms	Documents
L3 and (purity or pure or dosage or conc or concentration) adj5 (hht or homoharringtonine)	3

Prev Page Next Page Go to Doc#

PALM Intranet

Application Number SEARCH

IDS Flag Clearance for Application 10617927

IDS Information

Content	Mailroom Date	Entry Number	IDS Review	Reviewer
M844	09-07-2004	17	☑	01-30-2006 08:46:51 HLilling

UPDATE

STN

```
     FILE 'WPIDS, CAPLUS, USPATFULL, IFIPAT, TOXCENTER, DRUGU, BIOSIS, PASCAL'
     ENTERED AT 03:52:18 ON 30 JAN 2006
L4           14 S L3
L5            8 DUP REM L4 (6 DUPLICATES REMOVED)
                   ANSWERS '1-3' FROM FILE WPIDS
                   ANSWER '4' FROM FILE CAPLUS
                   ANSWERS '5-6' FROM FILE USPATFULL
                   ANSWER '7' FROM FILE TOXCENTER
                   ANSWER '8' FROM FILE DRUGU
```